

## REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on September 8, 2005 and allowance of the application.

Applicants acknowledge the withdrawal of the rejection of claim 27-34 under 35 U.S.C. 112, first paragraph.

Applicants acknowledge the withdrawal of the indicated allowability of present claims 17-26 as indicated in the previous Office Action dated July 6, 2004.

Applicant's note that their request under 37 C.F.R. 1.48(a)-(c) to correct the inventorship of the present application is acknowledged by the Examiner.

Applicants gratefully acknowledge the Examiner's acceptance of the correction of inventorship.

The Office action notes the submission of a newly executed declaration by inventors Nandan Koppiker and Eliot Forster accompanying the request under 37 C.F.R. 1.48(a) and 1.48(c) to correct the inventorship of the instant application.

The Office action objects to the Declaration for failing to set forth a mailing address for inventor Eliot Forster. The Office Action states that the Declaration does not identify the city and either state or foreign country of residence of this inventor. The Office Action states that the residence information may be provided on either an application data sheet or supplemental oath or declaration.

The Office Action requires appropriate correction.

Applicants herewith include a Supplemental Application Data Sheet.

The Office Action objects to Claim 29 for failing to conclude with a period.

Applicants have herein corrected claim 29.

Claims 17-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. (U.S. Patent No. 6,166,219; Issued December 2000, Filed November 1998) in view of Ellis et al. (WO 94/28902; 1994), Singh (WO 98/03167; 1998), Bueno et al. (U.S. Patent No. 6,127,418; Issued October 2000, Filed April 1999) and Stedman's Medical Dictionary (Twenty-Second Edition; 1972).

The rejection states that Yamasaki et al. teaches a pharmaceutical composition comprising a cGMP PDE5 inhibiting benzimidazole compound of the formula (I) or a

pharmaceutically acceptable salt thereof (col. 35, line 64-col.36, line 26) in combination with a pharmaceutically acceptable carrier (col. 37, line 65-col. 38, line 6) and further teaches a method of treating a disorder that is responsive to treatment with a cGMP PDE inhibiting compound of formula (I) or a pharmaceutically acceptable salt thereof (col. 35, lines 22-55) in a variable amount depending on the age, condition and type of disorder of the patent to be treated (col. 38, lines 16-20). The rejection also states that the disclosed composition can be administered orally in the solid form of tablets, granules, powders or capsules or in liquid forms, such as solutions, suspensions, syrups, emulsions or lemonades (col. 37, line 65-col.38, line 9). The rejection also states that Yamasaki et al. further teaches diabetic neuropathy as a medical condition responsive to treatment with the cGMP PDE5 inhibiting compounds (col. 1, lines 14-44, especially line 21).

The rejection acknowledges that Yamasaki et al. is silent as to the particular IC50 concentration or the selectivity ratio of the inhibitor. The rejection states that, however, in light of the fact that the particular type of compounds presently claimed are expressly disclosed in Yamasaki et al. and are recognized to function in the same manner as required by the present claims (co. 35, lines 22-55, especially lines 52-53), the IC50 concentration or the selectivity ratio of the inhibitor are not seen to differ between the prior art of Yamasaki et al and that of the present claims, absent factual evidence to the contrary (see present claims 19-20, 24-25 and 30-31).

The rejection states that the differences between the Yamasaki et al. reference and the presently claimed subject matter lie in that the reference does not teach:

- (i) the concomitant administration of gabapentin or pregabalin with the cGMP PDE5 inhibitor or the formulation of gabapentin or pregabalin in combination with the cGMP PDE5 inhibitor in the pharmaceutical composition (see present claims 17, 18, 22, 23, 27, 33 and 34);
- (ii) the particular use of sildenafil or its pharmaceutically acceptable salts as the cGMP PDE5 inhibitor (see present claims 21 and 32); and
- (iii) the treatment of diabetic polyneuropathy (see present claim 28).

The rejection states that however, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) The rejection states that it is acknowledged that Yamasaki et al. is silent as to the use of gabapentin or pregabalin in the disclosed composition administered for the treatment of diabetic neuropathy. The rejection states that however, both gabapentin and pregabalin were well known in the art to be useful for the same therapeutic purpose of treating diabetic neuropathy. The rejection states that Singh discloses the use of gabapentin or (s)-3-(aminomethyl)-5-methylhexanoic acid (also known as pregabalin; see Bueno et al., U.S. Patent No. 6,127,418, at col. 2, lines 50-55) for the treatment of diabetic neuropathy and further discloses a pharmaceutical composition comprising the active GABA compound in combination with an inert, pharmaceutically acceptable carrier for oral administration to mammals, including humans, suffering from such a condition by administering an effective amount of the compound (page 5, lines 9-19 and page 7, lines 4-20). The rejection states that it would, therefore, have been obvious to a person of ordinary skill in the art to employ either gabapentin or pregabalin in combination with a cGMP PDE5 inhibiting composition as disclosed by Yamasaki et al. because each compound was known in the art to be successful for achieving the same therapeutic effect. The rejection states that motivation to administer both compounds flows logically from the efficacy of each compound in treating diabetic neuropathy as demonstrated in the prior art and further because each compound has been previously for this same therapeutic objective. The rejection states that in the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA) and MPEP §2144.06.

(ii) The rejection states that it is acknowledged that Yamasaki et al. do not expressly teach the use of the cGMP PDE5 inhibitor sildenafil, or its pharmaceutically acceptable salts thereof, as a compound for treating diabetic neuropathy. The rejection states that however, Yamasaki et al. discloses that diabetic neuropathy is a condition responsive to treatment with a cGMP PDE, particularly a cGMP PDE5, inhibiting compound. The rejection states that in light of such a relationship, it would have been an obvious conclusion to one of ordinary skill in the art that the treatment of a condition

known to be responsive to a cGMP PDE5 inhibiting agent would not be solely limited to those compounds disclosed by Yamasaki et al., but that effective treatment of such a condition would have been reasonably expected to occur with any one or more other compounds known to exert the same effect (i.e., the inhibition of c GMP PDE5). The rejection states that the use of a cGMP PDE5 inhibitor compound, e.g., sildenafil, for the formulation of a pharmaceutical composition administered for the treatment of diabetic neuropathy would have been obvious to, and a matter well within the purview of, the skilled artisan. The rejection states that Ellis et al. teaches the compound 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one as a potent and selective inhibitor of cGMP-specific PDE5 (page 7, lines 1-3 and page 9, lines 1-3 of the last paragraph). The rejection states that the use of such a compound was well known in the art to exert inhibitor effects on cGMP-PDE5 and, therefore, would have been reasonably expected to demonstrate the same, or substantially similar, efficacy in treating diabetic neuropathy, as that shown by the benzimidazole cGMP-PDE inhibiting compounds expressly taught by Yamasaki et al.

(iii) The rejection states that although the present claims recite the use of a cGMP PDE5 inhibitor compound in combination with gabapentin or pregabalin for the treatment of diabetic polyneuropathy, while the cited references teach diabetic neuropathy, the distinction between diabetic polyneuropathy and diabetic neuropathy is not considered a patentable difference, absent factual evidence or direction to the contrary. The rejection states that the presence of the prefix "poly" amounts to nothing more than a quantification of the number of peripheral nerves that are affected by neuropathy resulting from diabetes. The rejection states that in this regard, Stedman's Medical Dictionary has been cited (1972; p. 1000) to show that polyneuropathy is defined as "a disease process involving a number of peripheral nerves." The rejection states that thus regardless of whether the neuropathic phenomenon effects one or more than one peripheral nerve(s), such does not change the fact that both cGMP PDE5 inhibitor compounds and gabapentin and pregabalin where known in the art for the treatment of neuropathy, in general. The rejection concludes that it would logically follow, therefore, that two compounds known to have efficacy in the treatment of diabetic

neuropathy occurring in one nerve would also be reasonably suggestive of having efficacy in treating diabetic neuropathy occurring in multiple nerves.

The rejection states that the prior art made of record and not relied upon is considered pertinent to applicant's disclosure and reference's U.S. Patent 6,251,904 to Bunnage et al. (Pyrazolopyrimidinone cGMP PDE5 Inhibitors for the Treatment of Sexual Dysfunction; Issued June 2001, Filed September 1999).

Applicants traverse the rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. (U.S. Patent No. 6,166,219; Issued December 2000, Filed November 1998) in view of Ellis et al. (WO 94/28902; 1994), Singh (WO 98/03167; 1998), Bueno et al. (U.S. Patent No. 6,127,418; Issued October 2000, Filed April 1999) and Stedman's Medical Dictionary (Twenty-Second Edition; 1972).

The *prima facie* case is a procedural tool, and requires that the examiner initially produce evidence sufficient to support a ruling of obviousness; thereafter the burden shifts to the applicant to come forward with evidence or argument in rebuttal. In re Kumar, 76 USPQ2d 1048 (CA FC 2005). Applicants submit that the rejection has not made out a *prima facie* case of obviousness and therefore has not shifted the burden to Applicant. Quite simply there is nothing in the Yamasaki et al. reference that links a cGMP-PDE-V mechanism with the treatment of diabetic neuropathy.

The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Laskowski, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

The rejection does not detail reasoning that provides the motivation to modify the prior art and thus the rejection does not present a *prima facie* case of obviousness. Specifically, it is believed that there are three separate distinct passages in the specification that are related to diabetic neuropathy and Applicants have carefully reviewed the passages with regard to their relationship to PDE5 inhibitors and provide the following description.

Specifically, the rejection does not detail reasoning that provides the motivation to modify the disclosure of the reference (col. 1, lines 14-44) from a disclosure of a

multitude of uses (including diabetic neuropathy) for certain benzimidazole derivatives to a disclosure of the use of certain PDE5 inhibitors for the treatment of diabetic neuropathy.

Specifically, in the passage, col. 1, lines 14-44 certain benzimidazole derivatives are suggested for preventing and treating a plethora of about five dozen disease/conditions. While one of the disease/conditions listed is diabetic neuropathy there is quite simply no motivation from this passage to utilize a cGMP-PDEV inhibitor for the treatment of diabetic neuropathy. The passage simply does not mention the cGMP-PDEV mechanism of action.

In addition, the rejection does not detail reasoning that provides the motivation to modify the disclosure (col. 35, lines 22-36) of the reference from a disclosure of certain benzimidazole derivatives as suggested for preventing and treating a plethora of about two dozen disease/conditions “based on their blood sugar level-depressing activity” to a disclosure of the use of certain PDE5 inhibitors for the treatment of diabetic neuropathy.

Specifically, in the passage, col. 35, lines 22-36 certain benzimidazole derivatives are suggested for preventing and treating a plethora of about two dozen disease/conditions “based on their blood sugar level-depressing activity”. While one of the disease/conditions listed is diabetic neuropathy there is quite simply no motivation from this passage to utilize a cGMP-PDEV inhibitor for the treatment of diabetic neuropathy. The passage simply does not mention the cGMP-PDEV mechanism of action. To the contrary, the passage emphasizes the mechanism of action as being “their blood sugar level-depressing activity”.

In addition, the rejection does not detail reasoning that provides the motivation to modify the disclosure (col. 35, lines 22-25 and lines 36-55) of the reference from a disclosure of certain benzimidazole derivatives as suggested for preventing and treating a plethora of disease/conditions based on several different mechanism of actions (without tying together each disease/condition and a particular mechanism of action) to a disclosure of the use of certain PDE5 inhibitors for the treatment of diabetic neuropathy

Specifically, in the passage, col. 35, lines 22-25 and lines 36-55, certain benzimidazole derivatives are suggested for preventing and treating a plethora of about three dozen disease/conditions. Importantly, the diseases are stated to be treated

based upon a variety of different mechanism of actions of the compounds. The list of mechanisms of action is at least six (it is clear that other isoforms of cGMP-PDE besides PDE-V inhibitors are also contemplated and this would raise the number of mechanisms of action to at least one dozen). There is simply no motivation to select the combination of disease/condition (i.e., diabetic neuropathy) and mechanism of action (i.e., cGMP-PDE-V inhibition) from the combined list of approx. three dozen disease/conditions and approx. one dozen mechanisms of action. Nor is there any reasonable expectation of success that the match-up of any particular disease/condition and mechanism of action is relevant or appropriate. Restated, it is simply not specified which pharmacological activity is useful in treating, or relates, to which disease.

Applicants further submit that at best the references relied on by the Examiner make Applicants' invention no more than "obvious to try", but that "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the references provide no effective motivation or suggestion that a PDE-V inhibitor could or should be tried in the treatment of diabetic neuropathy and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in these references, the references provide no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

The consistent criterion for determination of obviousness is whether the prior art **would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

As explained fully below, the art cited by the Examiner, at most, makes it no more than perhaps obvious to explore an area of research, and this is one of the classic hallmarks of an “obvious to try” rejection:

The admonition that ‘obvious to try’ is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...**In others, what was ‘obvious to try’ was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.**

In re O’Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988), emphasis supplied.

It is further noted that “[t]he issue of obviousness is determined entirely with reference to a hypothetical person having ordinary skill in the art. It is only that hypothetical person who is presumed to be aware of all the prior art. The actual inventor’s skill is irrelevant to the inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something -- call it what you will -- which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under section 103 by inquiring into what patentees (i.e. inventors) would have known or would likely have done, faced with the revelations of references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which. Standard Oil Co. V. American Cyanamid Co., 774 F.2d 448, 454 (Fed. cir. 1985).

For example, the passage, col. 35, lines 22-25 and lines 36-55, is simply a classic invitation to experiment to determine which disease/condition should be linked with a particular mechanism of action. At best this is an invitation to “explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.” At best Yamasaki et al. is an invitation to explore a variety of disease/conditions with certain mechanisms of action.



Further, even if the art is, *arguendo*, viewed as providing a suggestion, it clearly provides no reasonable expectation or likelihood of success. Thus, even if an argument could be made that the art provides a suggestion to explore the use of PDEV inhibitors to treat diabetic neuropathy, this amounts, perhaps, to inviting experimentation, i.e., to perhaps making testing PDEV inhibitors more obvious to try, which again is manifestly not the proper standard for patentability. O'Farrell, *supra*.

In addition, the Rejection references In Re Kerkhoven. Even assuming *arguendo* use of the two agents for the same purpose, which Applicant does not concede (see above discussion), the applicable case law specifically addressing the combination of two agents, each known individually for the same purposes fully supports the Examiner's failure to carry her burden of establishing *prima facie* obviousness. Thus, *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987) governs here and not, as the Examiner alleges, the older decision of *In re Kerkoven*, 626 F.2d 846 (CCPA 1980) (see also MPEP 2144.06). As the Federal Circuit held in *Geiger*, "at best" the combination proposed by the Examiner evidenced a general incentive to "try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 USC § 103." (2 USPQ2d at 1278). In *Geiger*, the components of the claim were broadly used in water treatment, albeit different aspects of water treatment: corrosion prevention and scale prevention. Appellant's claimed invention is even more unobvious than *Geiger* since an alpha 2 delta compound ligand and a PDE V inhibitor are different drugs used for different purposes functioning by different mechanisms (which further confounds the ability to guess at their effects if combined). But it is clear from *In re Geiger* that even if the compounds were broadly used for the same purpose that only evidences a general incentive to try various combinations.

Further, the rejection states that it would be obvious to employ either gabapentin or pregabalin in combination with a cGMP PDE5 inhibitor. This oversimplifies the combination of pharmaceutical agents. The Examiner appears to proceed from the assumption that it is a common technique in the pharmaceutical field to formulate ingredients, which have conventionally been contained in separate tablets, into a single formulation. This appears to take it for granted that any two known separate pharmaceutical agents can or should be combined. Again, this vastly oversimplifies the

position. Counterbalanced against the possibility of improved patient compliance there are many reasons why those skilled in the art would not pursue a particular combination. For example, there have been many examples of combination agents that have exhibited poor performance and even dangerous side effects. One example is the diet drug "PHEN-PHEN" (a combination of phentermine and fenfluramine) which resulted in damage to heart valves and was removed from the market. In addition, virtually all approved pharmaceutical agents have "drug-drug" interactions that restrict their use in combination with other pharmaceutical agents.

In the 1990s it had become widely recognized that drug interactions/combinations can result in unexpected effects. For example, there is a chapter in a widely used standard text, Remington: The Science and Practice of Pharmacy, 19<sup>th</sup> Edition, Chapter 105 (Drug Interactions, by DA Hussar), pages 1822 – 1836, edited by AR Gennaro, Mack Publishing Co. Easton, 1995, that outlines the state of knowledge at that time. Physicians and regulators had already at that time been sensitized to drug interaction issues by several highly publicized tragedies caused by drug interactions. These interactions occur at different levels, pharmacology and can impact both safety and efficacy of the interacting agents.

A pharmacological interaction is the result of combining drugs (such as gabapentin and a PDEV inhibitor), which act upon different factors. Accordingly, they may interact in a manner detrimental to the treatment of disease.

Restated agents which act upon different factors may not interact in a manner beneficial to the treatment of disease. Diabetic neuropathy and its progression are the result of a complex series of interconnecting factors which continue to be studied by the medical community. Gabapentin is an alpha 2 delta ligand which acts upon one factor known to contribute to diabetic neuropathy while a PDEV inhibitor acts upon a different and separate factor. In the complex system of factors that combine to produce heart disease and contribute to its progression, the combination of an agent useful in acting against one factor could just as easily cancel out the usefulness of a second agent useful in acting against a separate factor (assuming *arguendo* the reference teaches this).

Applicants enclose herewith a Supplemental Information Disclosure Statement.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

Date:

3/6/06



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